PROSTATE CANCER

CHAPTER 9

Minimally Invasive Ablative Therapies

Abbreviations and Acronyms

AP	= Anteroposterior
AS	=Active Surveillance
BDFS	= Biochemical Disease-Free Survival
cc	= Cubic Centimeters
ED	=Erectile Dysfunction
HIFU	= High Intensity Focused Ultrasound
LE	= Life Expectancy
mL	= Milliliter
mm	= Millimetre
mo	=Month
MRI	= Magnetic Resonance Imaging
ng/mL	=Nanogram per milliliter
ng	= Nanogram
PCa	=Prostate Cancer
PSA	=Prostatic Specific Antigen
RP	= Radical Prostatectomy
RT	= Radiation Therapy
QoL	=Quality Of Life
TRUS	=Transrectal Ultrasound
TURP	=Transurethral Resection Of Prostate
UTI	= Urinary Tract Infection
VTP	=Vascular Targeted Photodynamic Therapy

Section 1
Cryotherapy

Cryotherapy for prostate cancer is a minimally invasive procedure in which the prostate is frozen but not removed. It is done under general anesthesia, local anesthesia or regional anesthesia.

Cryotherapy has evolved from an investigational therapy to a possible alternative treatment for PCa for patients who are not fit for surgery or have a life expectancy < 10 years[1]. It is an out-patient procedure or may need 1 night hospitalization. Patient typically can resume normal lifestyle in 2-3 days. Characteristics of appropriate candidates for this procedure have been summarized in table 1.

Table1- Appropriate scenario for cryotherapy for PCa [1, 2, 3]

- Organ confined disease or minimal tumor extension beyond prostate
- Low or intermediate risk disease
- Prostate volume < 40 mL
- No History of TURP (Relative contraindication due to increased risk of urethral sloughing)
- Not a candidate or do not wish to undergo RP or RT

This is a relatively new treatment alternative. Patients with a LE > 10 years should be informed that there are no or only minimal data regarding cancer control at 10 and 15 years with this modality[1].

Different PSA nadirs have been used by different groups. A PSA nadir of ≤ 0.5 ng/mL results in a favorable biochemical disease-free survival especially in low-risk disease[2]. In spite of that, 5-year BDFS rates are inferior to those achieved by RP even in low-risk patients[1]. Patients should be informed accordingly. The 5-year actuarial BDFS rates in different risk groups using

PSA thresholds of < 0.5 ng/mL have been shown in table 2.

Table 2-The 5-year actuarial BDFS rates using PSA thresholds of < 0.5 ng/mL[1]

Risk group	The 5-year actuarial BDFS rate
Low risk	60%
Intermediate risk	45%
High risk	36%

Like other procedures, cryotherapy for prostate cancer may be associated with some complications. These complications have been summarized in table 3.

Table 3-Complications of cryotherapy for prostate cancer[1]

Complications	Probability (%)
ED	80
BOO needing TURP	5
Incontinence	4.4
Tissue sloughing	3
Rectal fistula	< 0.2

The urinary catheter may need to remain in place for about two weeks to allow for healing. A supra-pubic catheter may be inserted by some groups. As noted in above table, ED is common in men following cryotherapy for prostate cancer and this problem may persist long term. In case of failure, cryotherapy may be repeated or patients may undergo radiation therapy or radical prostatectomy.

Section 2

HIFU

High intensity focused ultrasound, cryotherapy and photodynamic therapy are the most commonly used minimally invasive treatments for localized prostate cancer. These treatments are well tolerated and are associated with decreased morbidity .However, long-term oncologic efficacy of these modalities remain to be determined [2]. Except for cryotherapy, these options are still experimental or investigational[1].

HIFU applies high-intensity focused ultrasonic energy via a transrectal probe to locally heat and destroy targeted tissue. HIFU is performed under general or spinal anaesthesia, with the patient lying in the lateral position[1]. The procedure is time-consuming, with about 10 gram prostate tissue treated per hour[1]. Characteristics of appropriate candidates for this procedure have been summarized in table 4.

Table 4- Appropriate scenario for HIFU for PCa[2, 4]

- T1-T2b disease
- Low to moderate risk disease
- Prostate volume <40cc
- AP dimension (measured by TRUS) <35 mm
- No calcifications > 1cm
- Patent urethra and bladder neck
- Rectum width ≥2 fingers

Patients with large prostates (> 40 cc) or those with significant voiding symptoms may require size reduction before procedure either by TURP or hormonal therapy. HIFU results and complications have been shown in table 5

and 6.

Table 5- HIFU results[5]

- Five-year disease-free survival rates ranged from 55% to 95%.
- The series (n = 140) with the longest follow-up (i.e., 6.4 years) reported a negative biopsy rate of 86.4% and a 5-year disease-free survival rate of 66%.

Table 6-HIFU complications[5]

Complications	Probability (%)
ED	44.5
Urethral stricture	12.3
Urinary incontinence	8.1
UTI	7.5
Urinary retention	5.3
Chronic perineal pain	3.4
Urethrorectal fistula	1

A catheter must be in place for approximately 2 weeks following treatment. Some men may need indwelling catheters longer than 14 days. A suprapubic catheter may be inserted by some surgeons. It is important to give bladder neck relaxants like Flomax prior to catheter removal. Subsequent TURP or bladder neck incision to treat bladder outlet obstruction is common[1].

Urinary incontinence is classified as grade 1, 2, or 3, depending on its severity. Grade 1 is minimal stress incontinence which happens only occasionally and occurs with severe straining. Grade 3 is severe or complete incontinence. Grade 1 incontinence may occur in <5% of cases. The probability of grade 2 and 3 incontinence is <1%.

Section 3
Focal Therapy for Low Risk Prostate Cancer

Prostate cancer screening has resulted in detecting lower risk cancers in younger men at an earlier stage of disease and is leading to over-detection and over-treatment in a significant number of patients[6]. Studies show that at least a quarter of men over age 55 have prostate cancer. However, only a small proportion of these men will actually go on to have clinical problems with the disease, and the risk of dying from it is extremely low [7]. Traditionally, the patient with a new diagnosis of localized prostate cancer faces either radical therapy, in the form of RP or RT, or may elect to follow AS program[2].However, the truth is that a growing subset of these men may not be willing to accept the psychological burden of active surveillance nor the side effects of extirpative or radiation therapy [2].

Focal therapy seeks to establish a middle ground between active surveillance and radical treatment[7]. Focal therapy may fill the gap between an active surveillance strategy and whole-gland treatment providing a reasonable balance between cancer control and QoL issues in the future[8, 9]

The aim of focal therapy is to ablate known cancer foci while trying to reduce collateral damages to the structures required for maintaining normal urinary and sexual function. In other words, the goal of focal therapy is to selectively ablate known disease, while minimizing lifetime morbidity without compromising life expectancy[10].

In fact, focal therapy for low risk prostate cancer is similar to lumpectomy for low risk, localized breast cancer and we may refer to it as male lumpectomy[11, 12]. The ideal patients for focal therapy appear to be ones with low-grade, low-volume disease that can be easily characterized[10]. It relies on modern imaging techniques as well as new minimally invasive procedure to ablate cancer foci. To truly perform focal therapy it is required not only to visualize the tumour on

imaging beforehand, but also to monitor the ablation in real time[11]. Different modalities like focal laser ablation, HIFU, cryotherapy and VTP (Vascular targeted photodynamic therapy) may be used for this purpose[10, 13, 14]. Cryotherapy and HIFU emerged as pioneers in focal therapy showed a lot of promise [10] .Early results with cryotherapy and HIFU appear encouraging, even if to date experience is limited and follow-up is immature[8]. Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials[1]. Rational for focal therapy for low risk prostate cancer, advantages and disadvantages of this therapy and modalities that may be used for localization of cancer foci are summarized in table 7-9.

Table 7- Rational for focal therapy for low risk prostate cancer[7, 8, 11, 15-18]

- Up to one-third of patients who presented initially with T1c disease have been found to have unifocal disease on examination of RP specimens.
- So, up to one-third of patients might be cured.
- In case of a multifocal disease, 92% of local spread comes from the dominant focus.
- It has been suggested that metastatic disease also comes from this dominant focus.
- The insignificant tumour, smaller than 0.5 mL, has very low propensity for extra capsular extension and metastasis.
- By destroying the dominant focus, we might decrease local extension and also prevent PCa from metastasis.

Table 8-Advantages and disadvantages of focal therapy for low risk PCa[8, 11]

Advantages	Disadvantages
• Minimal morbidity • Index tumor ablation • Might decreased mortality from cancer • Other treatment options are feasible afterward	• Very short-term data • Tumors outside ablated area may be left behind • Repeat biopsies are needed

It should be emphasized that this treatment will only be effective if applied in conjunction with a strategy of AS and repeat treatment when necessary.

Table 9- Localization of cancer foci for focal therapy [1, 7]

- Template-guided transperineal prostate biopsy may be ideally used to characterize the appropriate candidates.
- Multiparametric MRI may be alternatively used to localize cancer foci. This approach allows us to diagnose 80-85% of tumors in the prostate.

MR directed ultrasound guided laser focal thermotherapy and MR image guided robot assisted focal therapy of prostate cancer are new modalities in which multiparametric MRI and Indigo Optima laser are used to localize and destroy the prominent cancer foci.

These modalities rely on accurate localization of cancer within prostate and precise destruction of only that tumor. Eligible candidates have small, one site, low to intermediate risk disease[7].

Selected patients are put into the MRI scanner and sedated[7] .Using a specific software, needle will be inserted to exact site and then laser energy is used to ablate the cancer site[7].MRI is very temperature-sensitive, and one can watch in real time as the laser essentially burns the tumour without affecting anything around it[7]. Early results show that MRI-guided focal laser therapy of low-risk prostate cancer is feasible and may offer a good balance between cancer control and side effects[19].

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